REMARKS

Reconsideration and allowance of the application are respectfully requested in light of the foregoing amended claims and the following remarks.

The present application relates to a method of identifying compounds which resensitize cancer cells to the effects of chemotherapeutic agents. The chemosensitizing compounds identified by said method do not necessarily have the cytotoxic effects of chemotherapeutic agents. In particular, the chemosensitizing compounds identified by said method can resensitize cells to the cytotoxic effects of chemotherapeutic drugs and may be further used in combination with chemotherapeutic agents.

Claims 64, 65, 66, 67, 68 and 69 are pending in the application.

Claims 64, 65, 66, 67, 68 and 69 are new claims.

Claims 1 and 7 have been canceled in the current amendment.

The Examiner has rejected claims 1 and 7 under 35 USC 112 first paragraph as failing to adequately teach how to make and/or use the invention, and thereby failing to provide an enabling disclosure.

The Examiner has further rejected claims 1 and 7 wherein the instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Applicants believe the rejection can be withdrawn in view of new claims 64-69.

In response, applicant respectfully traverse the rejection of claims 1 and 7 because applicants believe the specification is enabling within the meaning of 35 USC 112. Applicants believe that the specification including the testing procedures in the present application enable the invention within the meaning of 35 USC 112 and provide clear guidance.

As presented in the specification on page 3, lines 34-35, "An important aspect of this invention is the capability to identify test compounds as chemosensitizing agents following evaluation in an assay of this invention."

As further presented in the specification on page 4, lines 5-14, "A further aspect of this invention is a method for identifying chemosensitizing compounds that reverse non P-gp/non MRP multiple drug resistance in cancer cells exhibiting non P-gp/non MRP drug resistance phenotype comprising administration of a test compound and a chemotherapeutic agent to which cancer cells are resistant and measuring cancer cell survival."

As an illustration of testing procedures and test results are those described in the specification and in Table 14 on page 33 where the test results of resensitizing S1-M1-3.2 Human Colon

Cancer Cells to Mitoxantrone and Toxicity of Fumitremorgin A, B and C and Diketopiperazines against S1-M1-3.2 are presented. The concentration of compounds, Fumitremorgin A, B, C and examples of Formula (I) at the doses described (μM) are toxic doses which kill more than 20% of the cells. When the same compounds are given with Mitoxantrone where the concentration of compound that kills 50% of the cells is less than the toxic doses which identifies these compounds as resensitizing the cells to the chemotherapeutic effects of Mitoxantrone.

To further illustrate the above, the ability of FTC to resensitize S1-M1-3.2 cells to mitoxantrone is shown in Table 7 where cells were incubated for three days with the indicated doses of FTC alone or in combination with 3.2 μM mitoxantrone. Cell survival is estimated using the SRB assay described on page 18 of the specification.

No toxicity of FTC alone was observed in the dose range tested (0.1-80μM). However, in combination with mitoxantrone, 50% of the cells were killed with 0.35 μM of the drug.

In further illustration of the test procedures and results with further antitumor agents the Examiner's attention is drawn to Table 10, in the specification on pages 27-28, where multiple antitumor agents are tested with the chemosensitizing compound FTC in multiple cell lines wherein the test data show an increase in reversal activity with mitoxantrone(93 fold), doxorubicin(26 fold) and topotecan(24 fold).

Applicants believe they have provided sufficient working examples.

Based on the foregoing, it is respectfully submitted that the present application contains more than sufficient description to enable the skilled artisan to carry out the method set forth in the claims without undue experimentation. Accordingly, withdrawal of the section 112 rejection is respectfully urged.

It is respectfully submitted that the new claims 64-69 in view of the experimental description and illustrated testing procedures and results of the specification are allowable.

The Examiner has rejected claims 1 and 7 under 35 USC 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants respectfully traverse the rejection under 35 USC 112 second paragraph. Applicants have added new claims 64-69 to remove the indefinite rejection. The new claims define the metes and bounds of the invention as defined in Table 6 with a difference score of 22%. It is respectfully submitted that new claims 64-69 define the invention and are allowable.

Finally claims 1 and 7 are rejected under 35 USC 103 as being unpatentable over Cui et al, Naito et al in view of the Merck Manual. This rejection is also respectfully traversed.

The Merck Manual points to combination therapies of anticancer drugs. However, there is no teaching that would point to the problem solved by the instant invention where the resensitizing compounds of the instant invention, which are not anticancer agents at the doses used, are used in combination with anticancer agents.

The instant invention is simply not a mixing or combination of two neoplastic agents. What the invention is however, is a method to identify chemosensitizing compounds which resensitize cancer cells which have enhanced resistance to chemotherapeutic agents and in particular to chemotherapeutic agents selected from mitoxantrone, doxorubicin, and topotecan.

Importantly the exemplified test compounds Fumitremorgin A, B and C and the diketopiperazines of Formula (I) are not chemotherapeutic agents at the dose used.

The Naito et al reference does not solve the problem that is solved by the instant invention. The Naito et al reference however describes an atypical cancer cell line resistant to adriamycin and the analysis of the decreased cellular level of DNA Topo II and an overexpression of MRP gene. The Naito et al art does not suggest that it would be desireable to proceed to make the combination of the instant invention.

The Cui et al reference describes the preparation of new diketopiperazine derivatives produced by the fungus Aspergillus fumigatus which includes fumitremorgin C. However, the Cui et al art does not suggest that it would be desireable to proceed to make the combination of the instant invention.

As described by the Examiner, "it is generally considered prima facie obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose."

In response, applicants have not combined compounds taught in the prior art to be useful for the same purpose. Applicants have however, discovered through the method of the invention chemosensitizing compounds which can be combined with chemotherapeutic agents to enhance the ability of the antitumor agents to increase cell death in cells which have drug resistance.

The prior art of the Merck Manual, Naito et al and Cui et al do not suggest, teach or provide guidance that it would be desirable to combine chemosensitizing compounds and chemotherapeutic compounds as described in the instant invention.

It is the applicants view that the Merck Manual, Naito et al and Cui et al neither anticipate nor render obvious the presently claimed invention. Applicant respectfully requests the Examiner to withdraw the Section 103 rejection.

In conclusion, applicants respectfully request that the Examiner enter the amendment, reconsider the rejections in light of the remarks herein, amendments to the claims, added new claims and allow the application. Favorable treatment is earnestly solicited.

Respectfully submitted,

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